DETAILED ACTION

Restriction/Election

1. In response to the communication received on Nov. 6, 2008, from Doran R. Pace, the election without traverse of group XVIII, claims 9-12, 19 (in part), 45 (in part), wherein the large subunit is HS33, is acknowledged. Claims 1-26, 31-38, 43-45, 60-67, 72, and 86 are pending in this Application. Claims 4-6, 13-16, 20-26, 60-67, and 86 are withdrawn for being directed to non-elected inventions. Claims 9-12, 19 (in part), 45 (in part) along with linking claims, claims 1-3, 7, 8, 17, 18, 31-38, 43, 44, and 72 are examined in this Office Action.

Information Disclosure Statement

2. The listing of references in the specification on pages 35-40 is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Oath/Declaration

3. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

Non-initialed and/or non-dated alterations to the inventor's address have been made to the oath or declaration that was submitted on Oct. 10, 2006. See 37 CFR 1.52(c).

Specification

4. The specification is objected to because the Brief Description of the Drawings does not include the sequence identifiers associated with the amino acid sequences depicted in figure 1. Figure 1 includes the Mss sequence, the Pss sequence, and the Consensus sequence; and therefore the description of the drawings should include three different sequence identifiers for Figure 1. Applicant is advised to include the SEQ ID NOs: with the Brief Description of the Drawings. If the sequences in the drawings do not already have sequence numbers assigned to them, then a sequence number must be assigned, and a new sequence listing must be submitted. The new sequences in the sequence listing must be identical to the sequences disclosed in the figures, and applicant is cautioned to avoid any new matter. The consensus sequence should have Xs for the non-conserved amino acid residues.

5. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested: - - HEAT STABLE VARIANTS OF THE MAIZE ADENOSINE DIPHOSPHATE GLUCOSE PYROPHOSPHORYLASE SMALL SUBUNIT - - .

Claim Objections

6. Claims 43 and 72 are objected to because of the following informalities: they do not use a proper article when referring to the polynucleotide of claim 1. Applicant is advised to replace "a polynucleotide as defined in claim 1" with - - the polynucleotide as defined in claim 1 - - . Appropriate correction is requested.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-3, 7-12, 17-19, 31-38, 43-45, and 72 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point

out and distinctly claim the subject matter which applicant regards as the invention. All dependent claims are included in these rejections.

The term "relative to a wild type AGP enzyme" in claim 1 is a relative term which renders the claim indefinite. The term "relative to a wild type AGP enzyme" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. This is particularly true because the heat stability of different wild type AGP enzymes is drastically different with the AGP enzyme from potato being quite stable compared to the AGP enzyme from maize. Therefore, it is unclear which type of wild-type AGP enzyme the increased heat stability is relative to.

Furthermore, the claim construction makes it unclear if the “or a fragment thereof” is required to comprise a mutation and if the “fragment” is required to exhibit increased heat stability when expressed with a large subunit. The current claim construction seems to include the functional language only for the small subunit, with no functional limitations directed to the “fragment thereof”.

8. Claims 1-3, 7, 9, 17-19, 31-38, 43-45, and 72 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a nucleic acid comprising a polynucleotide encoding a mutant small subunit with a Y36C substitution relative to SEQ ID NO:2 wherein when said mutant small subunit is

expressed with a large subunit of a plant AGP enzyme to form a heterotetrameric enzyme, said heterotetrameric enzyme exhibits increased heat stability relative to the wild type maize AGP enzyme, does not reasonably provide enablement for nucleic acids encoding any mutant enzymes other than those that have a cysteine substituted for the tyrosine normally found at position 36 in the maize wild type small subunit nor does it reasonably provide enablement for mutant enzymes with increased heat stability relative to any wild type AGP enzyme other than the maize wild type enzyme nor does it reasonably provide enablement for a mutant small subunit of any heat labile plant enzyme other than the maize AGP enzyme. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claimed invention is not supported by an enabling disclosure taking into account the *Wands* factors. *In re Wands*, 858/F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988). *In re Wands* lists a number of factors for determining whether or not undue experimentation would be required by one skilled in the art to make and/or use the invention. These factors are: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples of the invention, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claim.

The claims are broadly drawn to a polynucleotide encoding a mutant small subunit of a heat labile plant ADP glucose pyrophosphorylase (AGP) enzyme, wherein when said small subunit is expressed with a large subunit of a plant AGP enzyme to form a mutant enzyme, said mutant enzyme exhibits increased heat stability relative to a wild type AGP enzyme and to plants, compositions and expression constructs comprising said polynucleotide

Applicants teach polynucleotides encoding mutant AGP small subunits having a cysteine substituted for the tyrosine that is normally found at position 36 in the wild type maize AGP small subunit (Y36C); wherein the resulting AGP enzyme has increased heat stability relative to the wild-type maize AGP enzyme (see Table 3 on page 31). This includes mutant AGP small subunits that had an additional amino acid inserted between residues 34 and 35 of the wild-type maize small subunit in addition to the Y36C substitution.

Applicants do not teach any heat stabilized AGP subunits that did not have a cysteine substituted for the tyrosine that is normally found at position 36 in the wild type maize AGP small subunit, nor did they teach any mutants that had an increase in stability relative to non-maize wild-type AGP enzymes, nor did they teach any heat labile plant AGP enzymes other than the maize AGP enzyme.

For example, in the prior art (Plant Physiology (1995) Vol. 109; pp. 245-251), Ballicora et al teach that the N terminus of the small subunit from the potato AGP enzyme is important for its heat stability (see right column on page 248), however

the increase in heat stability was relative to a truncated version of the AGP enzyme, it was not relative to the heat stability of the potato wild-type enzyme. Furthermore, in the prior art (Biochem. Biophys. Res. Comm. (1999) Vol. 257; pp. 782-786), Ballicora et al teach that the heat stability of the potato AGP is the result of di-sulfide bonds formed from a cysteine residue in the small subunit (see paragraph bridging pages 783-784). For this reason, mutations that do not add a cysteine residue to facilitate formation of di-sulfide bonds are highly unlikely to increase the heat stability of the maize heat labile AGP enzyme.

Given the lack of guidance in the instant specification, undue trial and error experimentation would be required for one of skill in the art to identify heat labile AGP enzymes other than the maize wild-type enzyme or for one of skill in the art to identify mutations, other than addition of cysteine residues in the N-terminus of the small subunit of the maize AGP enzyme that would result in an increase in heat stability of the enzyme. It would also require undue trial and error experimentation for one of skill in the art to identify mutations that would result in an increase in heat stability relative to wild-type potato AGP which is already quite heat stable.

Therefore, given the breadth of the claims; the lack of guidance and working examples; the unpredictability in the art; and the state-of-the-art as discussed above, undue experimentation would be required to make and use the claimed invention, and therefore, the invention is not enabled throughout the broad scope of the claims.

9. Claims 1-3, 7, 9, 17-19, 31-38, 43-45, and 72 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are broadly drawn to a polynucleotide encoding a mutant small subunit of a heat labile plant ADP glucose pyrophosphorylase (AGP) enzyme, wherein when said small subunit is expressed with a large subunit of a plant AGP enzyme to form a mutant enzyme, said mutant enzyme exhibits increased heat stability relative to a wild type AGP enzyme and to plants, compositions and expression constructs comprising said polynucleotide

Applicants describe polynucleotides encoding mutant AGP small subunits having a cysteine substituted for the tyrosine that is normally found at position 36 in the wild type maize AGP small subunit (Y36C); wherein the resulting AGP enzyme has increased heat stability relative to the wild-type maize AGP enzyme (see Table 3 on page 31). This includes mutant AGP small subunits that had an additional amino acid inserted between residues 34 and 35 of the wild-type maize small subunit in addition to the Y36C substitution.

Applicants do not describe any heat stabilized AGP subunits that did not have a cysteine substituted for the tyrosine that is normally found at position 36 in

the wild type maize AGP small subunit, nor did they describe any mutants that had an increase in stability relative to non-maize wild-type AGP enzymes, nor did they describe any heat labile plant AGP enzymes other than the maize AGP enzyme.

The essential features of the instant invention are that mutant enzyme comes from a heat labile plant AGP, and that the mutant enzyme has an increase in heat stability relative to a wild type AGP enzyme (see claim 1).

In the prior art (Plant Physiology (1995) Vol. 109; pp. 245-251), Ballicora et al teach that the N terminus of the small subunit from the potato AGP enzyme is important for its heat stability (see right column on page 248), however the increase in heat stability was relative to a truncated version of the AGP enzyme, it was not relative to the heat stability of the potato wild-type enzyme. Furthermore, in the prior art (Biochem. Biophys. Res. Comm. (1999) Vol. 257; pp. 782-786), Ballicora et al teach that the heat stability of the potato AGP is the result of di-sulfide bonds formed from a cysteine residue in the small subunit (see paragraph bridging pages 783-784). For this reason, mutations that do not add a cysteine residue to facilitate formation of di-sulfide bonds are highly unlikely to increase the heat stability of the maize heat labile AGP enzyme.

The Federal Circuit has recently clarified the application of the written description requirement to inventions in the field of biotechnology. The court stated that, "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within

the scope of the genus or of a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus." See *University of California v. Eli Lilly and Co.*, 119 F. 3d 1559; 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

The Applicants fail to describe a representative number of heat labile plant AGP enzymes. The Applicants only describe the maize AGP enzyme as being heat labile. The Applicants fail to describe a representative number of mutant small subunits that result in an increase in stability relative to any wild-type AGP enzyme. The Applicants only describe mutants with increased stability relative to the wild-type maize AGP enzyme. The Applicants fail to describe a representative number of mutant small subunits with mutations across the N-terminal portion of the small subunit, wherein the mutations result in an increase in heat stability. The Applicants only describe mutants that have a cysteine substituted for the tyrosine that is normally found at position 36 in the wild type maize AGP small subunit. Furthermore, the Applicants fail to describe structural features common to members of the claimed genus of heat-stabilized small subunits. Hence, Applicants fail to meet either prong of the two-prong test set forth by *Eli Lilly*. Furthermore, given the lack of description of the necessary elements essential for increasing the heat stability of the AGP enzyme, it remains unclear what features identify mutant small subunits capable of such activity. Since the genus of small subunits with mutations in the N-terminus that increase the heat stability of the

enzyme has not been described by specific structural features, the specification fails to provide an adequate written description to support the breadth of the claims.

Nucleic acids that encode mutant small subunits of AGP encompass multitudes of molecules, many of which would not encode heat-stabilized AGP enzymes when co-expressed with an AGP large subunit in a plant cell, and most of which were not in the Applicant's possession at the time of filing. The Applicants have reduced to practice only three mutants that demonstrate increased heat stability relative to wild-type maize AGP, all of which have a cysteine substituted for the tyrosine that normally appears at position 36 in the wild-type maize small subunit. Accordingly, the specification fails to provide an adequate written description to support the genus of nucleic acids encoding mutant small subunits of heat labile AGP enzymes that have increased heat stability relative to wild-type AGP enzymes as set forth in the claims. (See Written Description guidelines published in 2008 online at http://www.uspto.gov/web/menu/written.pdf).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 1-3, 7-12, 31, 43, and 72 are rejected under 35 U.S.C. 102(b) as being anticipated by Ballicora et al (Plant Physiology (1995) Vol. 109; pp. 245-251).

The claims are drawn to a polynucleotide encoding a mutant small subunit of a heat labile plant ADP glucose pyrophosphorylase (AGP) enzyme, or a fragment thereof, wherein when said small subunit is expressed with a large subunit of a plant AGP enzyme to form a mutant enzyme, said mutant enzyme exhibits increased heat stability relative to a wild type AGP enzyme and to plants, compositions and expression constructs comprising said polynucleotide. As discussed in the rejection under 35 USC 112, 2nd paragraph, above, it is unclear if the "fragment thereof" is required to have any of the functional limitations that are recited in the claims. The Examiner is broadly interpreting this to encompass fragments that do not need to have the recited functionality.

Ballicora et al teach polynucleotides encoding a protein that comprises "SP" (serine – proline) (see Table 1, deduced amino acid sequence form potato cDNA - fourth and fifth amino acids). The instant amino acid sequence of wild-type maize AGP small subunit includes "SP" at positions 10 and 11, therefore "SP" is a "fragment" of the maize AGP small subunit which is heat labile. None of the extra limitations in any of these claims are relevant to the "fragment thereof", therefore, they do not provide limitations that exclude Ballicora et al.

Ballicora et al teach E. coli that comprise an expression construct comprising this polynucleotide (see page 247); and E. coli are "cells" as required by claim 31.

They teach an E. coli strain comprising two plasmids, one encoding this "fragment" and one encoding the AGP large subunit from potato (see page 247); and this strain is a composition as required in claim 43.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 1, 2, 17-19, 31-38, 43-45, and 72 are rejected under 35 U.S.C. 103(a) as being unpatentable over Greene et al (PNAS (1998) Vol. 95; pp. 13342-13347) in view of Giroux, M. (US Pre-Grant Publication US 2003/0150027; for application no. 10/116,868, filed on April 5, 2002, with priority to 09/516,250, filed on Mar. 1, 2000) and further in view of Ballicora et al (Biochem. Biophys. Res. Comm. (1999) Vol. 257; pp. 782-786).

The claims are drawn to a polynucleotide encoding a mutant small subunit of a heat labile plant ADP glucose pyrophosphorylase (AGP) enzyme, wherein when said small subunit is expressed with a large subunit of a plant AGP enzyme to form a mutant enzyme, said mutant enzyme exhibits increased heat stability relative to a

wild type AGP enzyme and to plants, compositions and expression constructs comprising said polynucleotide.

Greene et al teach mutations in the large subunit of the maize AGP enzyme that result in enhanced heat stability (see entire article). They specifically teach one that is referred to as HS33 (see left column on page 13344). They teach a comparison of large subunit sequences from maize, wheat, barley, rice, and potato (see Figure 2 on page 13344).

Green et al do not teach mutations in the small subunit of a heat labile AGP enzyme. Nor do they teach transgenic plants expressing mutant small subunits or a polynucleotide that encodes both a small subunit and a large subunit.

Giroux teaches transgenic plants expressing a mutant form of AGP (see entire document) including both monocots (see claim 41) and dicots (see claim 45); with specific suggestions for wheat (see examples 1 and 2 on pages 15 and 16), rice (see paragraph 0220 on page 17), and pea (see paragraph 0221 on page 17).

Ballicora et al teach that a cysteine at the N-terminus of the potato AGP small subunit is important for the heat stability of the enzyme and that di-sulfide bonds formed from a cysteine residue in the small subunit are important for this stability (see paragraph bridging pages 783-784).

At the time the invention was made, it would have been obvious and within the scope of one of ordinary skill in the art to make mutations in the maize AGP small subunit to introduce cysteine residues in the N-terminus with the goal of

providing the necessary SH group for forming di-sulfide bonds to increase the heat stability of the enzyme. Given the teachings of Giroux that AGP is the rate limiting step in starch biosynthesis in plants (see paragraph 0011 on page 1), and the teachings of Giroux demonstrating that increasing the amount of AGP provides an increase in seed production and biomass production (see paragraph 0022 on page 1; and see experimental results in Table 1 on page 16), one would have been motivated to increase the amount of AGP in a transgenic plant. Given the teaching of Ballicora et al that di-sulfide bonds via cysteine residues in the N-terminal region of the small subunit can result in an increase in heat stability, one would have been motivated to substitute cysteine residues or to insert cysteine residues into the maize small subunit with a goal of increasing the heat stability of the AGP. Given the success of Greene et al in expressing mutant forms of the AGP large subunit that have increased heat stability, and given the success of Ballicora et al in producing transgenic plants with increased seed production and biomass production by increasing the amount of AGP, one would have had a reasonable expectation of success in expressing mutant maize AGP small subunits with increased heat stability that would result in an increase in seed production and biomass.

The additional limitations of co-expressing both the mutant small subunit and a large subunit from the same polynucleotide are obvious variations of what was taught in the art. The experiments by Ballicora et al utilize two separate plasmids to express the small subunit and large subunit; however, bi-cistronic

expression vectors for co-expression of two polypeptides in plant systems were well known in the art at the time of filing (for example, co-expression of the heavy chain and light chain of an antibody; or for example, expression of a protein of interest in addition to a selectable marker). For this reason, a polynucleotide that encodes both the mutant small subunit and the large subunit is an obvious variation.

12. No claim is allowed.

Allowable Subject Matter

13. The Examiner suggests the following claim language: - - A nucleic acid comprising a polynucleotide encoding a mutant small subunit of an ADP glucose pyrophosphorylase (AGP) enzyme, wherein said mutant small subunit comprises a substitution of a cysteine for the tyrosine at position 36 of the wild-type maize small subunit, and wherein said mutant small subunit optionally further comprises an insertion of an amino acid between the serine at position 34 and the threonine at position 35 of the wild-type maize small subunit. - -

Although the prior art suggests mutations that would substitute or add cysteine residues at the N-terminus of the maize AGP small subunit (see rejection under 35 USC 103, above), the prior art does not teach or suggest a substitution, specifically, of a cysteine for the tyrosine at position 36 of the wild-type maize AGP small subunit.

It is the Examiner's position that the recommended claim language, above, would be free of all of the rejections of record. If the Applicant confirms that SEQ ID NOs: 4, 8, and 10 each are mutant subunits with a cysteine for the tyrosine at position 36 of the wild-type maize small subunit, and optionally an insertion of an amino acid between the serine at position 34 and the threonine at position 35 of the wild-type maize small subunit, then all of these sequences could be rejoined for comprising a shared special technical feature, and for being "linked" by an allowable claim (ie. the recommended claim language).

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cathy K. Worley whose telephone number is (571) 272-8784. The examiner is on a variable schedule but can normally be reached on M-F 10:00 - 4:00 with additional variable hours before 10:00 and after 4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anne Marie Grunberg, can be reached on (571) 272-0975. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Cathy K. Worley/
Primary Examiner, Art Unit 1638